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L3: Entry 1 of 1 File: USPT Apr 21, 1992

US-PAT-NO: 5106615
DOCUMENT-IDENTIFIER: US 5106615 A

TITLE: Eyedrops having non-Newtonian rheological properties

DATE-ISSUED: April 21, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dikstein; Shabtay	Jerusalem			IL

APPL-NO: 07/ 620102 [PALM]
DATE FILED: November 30, 1990

PARENT-CASE:

STATUS OF APPLICATION

The present application is a continuation-in-part application of abandoned U.S. patent application Ser. No. 07/350,286 filed May 11, 1989, which is a continuation-in-part application of abandoned U.S. patent application Ser. No. 07/107,575 filed Oct. 13, 1987.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
IL	80298	October 14, 1986

INT-CL: [05] A61K 31/78, A61K 31/74

US-CL-ISSUED: 424/78.04; 514/912, 424/78.31, 424/78.32
US-CL-CURRENT: 424/78.04; 424/78.31, 424/78.32, 514/912

FIELD-OF-SEARCH: 424/81, 424/78, 514/912

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4540568	September 1985	Tragar et al.	574/912
☐	4620979	November 1986	Schachar	574/912

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
8404680	December 1984	WO	514/912
8404681	December 1984	WO	514/912

OTHER PUBLICATIONS

Survey of Opthalmology, vol. 22, No. 2, Sep.-1977, pp. 69-87, Holly et al.

ART-UNIT: 152

PRIMARY-EXAMINER: Page; Thurman K.

ASSISTANT-EXAMINER: Kulkosky; Peter F.

ATTY-AGENT-FIRM: Browdy and Neimark

ABSTRACT:

Isotonic humectant eyedrops which have pronounced non-Newtonian rheological properties, simulating the rheological behavior of human tears. The eyedrops are of value in the treatment of various abnormal states of the eye such as dry eye syndrome. They can also serve as carrier for a variety of pharmaceutically active ingredients. Essential components are in combination water, an anionic polymer having a M.W. in the 500,000 to about 4,000,000 range at a concentration so that the viscosity measured at a 1 sec.sup.-1 shear rate does not exceed about 150 cp. and a low molecular weight (of 500 or less M.W.) humectant polyol at a concentration of about isotonicity or slightly above. The solution must contain less than about 1.5 mM salt calculated as sodium chloride, not including the salts of the anionic polymeric viscosity enhancer, as higher concentrations destroy the non-Newtonian rheological properties. A process for treating dry eye syndrome by application of such eyedrops.

9 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 4

BRIEF SUMMARY:

1 FIELD OF INVENTION

2 The invention relates to isotonic humectant aqueous ophthalmic solutions which are of use in ophthalmology, and especially in cases of dry eye syndrome. They are also of value in the treatment of a variety of eye diseases and especially in infectious diseases etc.

3 The ophthalmic solutions contain in combination an effective humectant, generally in isotonic concentration, and an anionic polymer which is used to obtain a predetermined viscosity, the solutions being characterized by a non-Newtonian rheology. The viscosity decreases in a pronounced manner upon application of a mechanical force, as is the case during the blinking of a human eye: the decrease is at least by a factor of 2 times and preferably by a factor of 3 to 4. The viscosity of the natural tear film decreases in a

pronounced manner upon application of mechanical shear, see A J Bron, Prospects for the dry Eye; Trans Ophthalmol. Soc 104 (1985) 801-826.

4 It has been surprisingly discovered that the presence of salt, such as sodium chloride, destroys the non-Newtonian rheology, and thus it is stipulated that the solutions of the invention ought not to contain more than about 0.01 weight per cent.

5 The non-Newtonian rheological behavior of human tears has been described in Hamano and Mitsunaga, Japan J. Ophthalmol. (1973) 17, 209-299 and in Dudinski et al., Curr. Ther. Res. February 1983, 33, 322-337.

6 The novel eyedrops are especially useful in cases of dry eye syndrome.

7 To the best of the knowledge of the inventor there have not been known before eyedrops which combine highly effective humectant properties and a non-Newtonian rheology resembling that of human tears, i.e. eyedrops of low viscosity which substantially decreases upon application of a mechanical force.

8 BACKGROUND OF THE INVENTION

9 Various eye diseases require treatment by the application of liquid preparations, administered to contact the eye. Eyedrops are also frequently required by wearers of contact lenses. Dry eye disease is a serious condition which requires the repeated application of eye drops per day. Conventional eye drops are based on isotonic solutions of various inorganic salts, with or without "non-ionic" substances (see U.S. Pat. No. 4,409,205), frequently with an added high-molecular weight substance which increases the viscosity of the drops.

10 Amongst frequently used polymeric substances there may be mentioned methyl cellulose, hydroxy ethyl cellulose, polyvinyl alcohol, polyvinylpyrrolidone, hyaluronic acid, and the like. The viscosity is generally 1 cp to 30 cp.

11 It is known that at a viscosity of about above 15 cp a discomfort is experienced by most persons, see Adler C. A. et al. The Effect of Viscosity of the Vehicle on the Penetration of Fluorescein into the Human Eye, Exp. Eye Res. 11, 34-42 (1971) and Patton T. F. et al., Occular Evaluation of Polyvinyl Vehicle in Rabbits, J Pharm Sci. 64, 1312-1316, 1975. In view of this most eyedrops have a viscosity in the 2 cp to 5 cp range, even when it is known that a higher viscosity will result in a prolonged action. Therefore, isotonic solutions containing inorganic salts have drawbacks as regards viscosity and physiological characteristics, as solutions containing salts above a certain level do not undergo changes of viscosity upon application of a shear force.

12 Shively describes in U.S. Pat. No. 4,409,205 Ophthalmic Solutions, which have a salt (sodium chloride) content of from 0.1 weight per cent to about 7.5 weight per cent, in combination with a non-ionic polymer. Extensive experiments have shown that non-ionic polymers do not give solutions having non-Newtonian rheological properties. Furthermore, the salt content which is much above the upper limit stipulated according to the present invention would destroy any such properties, if these would have been present. It is clear that Shively did not intend to prepare non-Newtonian solutions, and he did never obtain such solutions by chance as his ingredients preclude such rheological properties.

13 Gressel, in WO 94/04681, provides a liquid ophthalmic composition comprising a polyanionic polymer for use as a long-lasting artificial tear. His product, as exemplified and as claimed, relates to a viscous liquid preparation containing 0.05% to 0.5 by weight of a polyanionic polymer in combination with sodium chloride as preferred tonicity agent. He actually exemplifies gels as evident from the viscosity data of all examples. The high sodium chloride content of Gressel will destroy non-Newtonian properties of all the compositions of the present invention.

14 The preparations of the present invention overcome to a large extent the drawbacks of this kind, since they have a certain viscosity at a low shear rate, which shear rate corresponds to that of an open eye, while when the eye blinks the viscosity of the composition decreases in a pronounced manner to the comfortable range of about 2 cp to about 15 cp, which mimics the behavior of natural tears.

15 None of patents WO 84/04861--Alcon, U.S. Pat. No. 4,620,979--Schachan or U.S. Pat. No. 4,540,568--Trager describe eye drops which are humectants and the viscosity of which is markedly shear dependent.

16 SUMMARY OF THE INVENTION

17 There are provided humectant isotonic eyedrops for the treatment of, and for the alleviation of the symptoms of dry eye syndrome. The novel eyedrops have a low viscosity and can easily be applied. They have non-Newtonian rheological properties, and upon application of a mechanical force their viscosity changes at least by a factor of two-fold: such mechanical force reduces the viscosity by a factor of at least 2, and preferably by a factor of 3. The unique humectant and rheological properties of the novel eyedrops are the result of a combination of a number of essential constituents, which are a high molecular weight, of the order of about 500,000 to about 5,000,000 and preferably in the range of 1,000,000 to about 2,000,000, anionic polymer, in such a concentration that the solution has a viscosity not above 150 cp measured at a shear rate of 1 sec.sup.-1, as efficient humectant a low molecular weight (less than about 500 M.W.) polyol having strong water holding properties, which is used at a concentration corresponding to isotonicity of the tears or varying from isotonicity by up to about 10 per cent; it being stipulated that the aqueous eyedrop solution contains less than about 1.5 milli-mole (mM) of salt calculated as sodium chloride, not including the salts of the anionic viscosity enhancing polymer.

18 A preferred humectant polyol is glycerol. There can also be used humectant low molecular weight polyols, such as polyalkylene glycols. When the mechanical shear force is applied, as is the case during the blinking of an eye, the viscosity decreases by a factor of at least twofold, and preferably by a factor from three to four. Examples of such decreases are illustrated in enclosed FIGS. 1 and 2.

19 As stated above the viscosity at a low shear rate ought not to exceed about 150 cp; the preferred range of viscosity is up to about 120 cp, and a still more preferred range is from about 10 to about 70 cp at a shear rate of 1 sec.sup.-1. When such an ophthalmic solution is applied to the human eye, no discomfort is experienced. When eye-blinking takes place, the mechanical force thus applied to the solution rapidly decreases its viscosity in a pronounced manner, and this prevents any discomfort.

20 The isotonic solutions of the invention can be used as carriers for various

pharmaceutically effective agents, such as antimicrobials, antiviral agents and the like.

21 Amongst preferred high molecular weight anionic polymers, used as viscosity enhancing agents, are high molecular weight polyacrylates. Some of these are marketed under the trade designation of Carbomer, the most preferred being Carbomer 941; produced from anionic monomers. There may also be used a suitable hyaluronic acid as viscosity enhancer, having preferably a molecular weight of 1,000,000 to 2,500,000.

22 According to the present invention there is generally used less than 0.1 weight-% of the anionic polymer. In the case of hyaluronic acid alone this may be as high as 0.3 per cent, and is preferably about 0.1%. With polyacrylic polymers the concentration is generally less than about 0.05, and this gives the desired viscosity, as defined above. The concentration is always adjusted according to the molecular weight and the required viscosity:

DRAWING DESCRIPTION:

The invention is illustrated with reference to the enclosed Figures, in which:

FIG. 1 is a graph of salt content versus viscosity at various shear rates;

FIG. 2 is a graph illustrating the rheological properties of the formulations according to the Examples;

FIG. 3 illustrates the moisturizing effect of 2 per cent by weight polyethylene glycol versus the molecular weight of the polyethylene glycol, and the effect of glycerol;

FIG. 4 illustrates the rheological properties of the composition according to Example 1 of U.S. Pat. No. 4,409,205 (Newtonian behavior).

DETAILED DESCRIPTION:

1 DETAILED DESCRIPTION

2 There are provided isotonic eye drops for the treatment of, and for the alleviation of the symptoms of dry eye syndrome. The novel eye drops have advantageous properties as compared with conventional eye drops. The novel eye drops are based on the use of a humectant such as glycerol, or other physiologically acceptable humectant polyols, such as polyethyleneglycol of M.W. not above 500, and anionic viscosity enhancer, and they are charactered by a change of viscosity upon application of a mechanical shear force. When at rest, the viscosity is constantly larger than when a shear force is applied. Thus, when eye-blinking takes place, the viscosity decreases and no discomfort is caused to the person who has applied such eyedrops. The change of viscosity upon application of a shear is brought out by the enclosed drawings.

3 Such isotonic solutions can be used as carrier for various types of medications used in ophthalmology. They can be used, amongst others, as carrier for various antimicrobial agents (antibiotics, antiviral agents and the like). The glycerol, as well as the other substances used according to the present invention are by themselves humectant, i.e. they are capable of

holding water.

4 The ophthalmic preparations according to the invention ought to include conventional adjuvants and auxiliaries, so as to prevent their deterioration storage. These are well known in the art and not indicated in the specific examples. Furthermore, in order to have proper viscosity, a suitable polymer has to be used.

5 Preferably the viscosity of the eyedrops is adjusted so as not to exceed about 40 cp to 70 cp at rest. The measurements are made at a very slow rate. When the eye blinks, the viscosity must go down rapidly to a lower value, preferably not to exceed about 15 cp and even lower. The eyedrops of the invention have this property of a rapid decrease of viscosity upon application of mechanical shear. Such non-Newtonian behavior decreases if a salt content is present in excess of about 1.5 millimole per liter of salt. This does not include salts of the anionic type viscosity enhancing agents. The shear rate with an open eye is to be about 1 sec.sup.-1 ; whereas upon blinking this changes dramatically to a value of above 1000 sec.sup.-1. Especially advantageous results were obtained by the use of hyaluronic acid or polyacrylate, either by itself or in combination with other physiologically acceptable high molecular weight substances. The eye drops are based on physiologically acceptable humectant. Humectants of choice are glycerol and other acceptable humectant polyols. These are organic non-ionic substances and very good results were obtained by the use of these.

6 The humectant properties of the preparations of the present invention are easily demonstrated by applying isotonic solutions of the invention to the skin of the forearm and by measuring the electrical conductivity, or capacitance of the stratum corneum resulting within half an hour after such application. An increase of such conductivity or capacitance is indicative of a humectant effect.

7 The humectants are always used in the form of an essentially isotonic solution. The eye drops are sterilized and, if required, suitable agents are added to prevent bacterial or fungal deterioration.

8 There were tested solutions of this type for treating dry eye disease. There were also prepared ophthalmic preparations comprising antimicrobials and antiviral agents wherein the carrier was an isotonic solution defined above.

9 FIG. 1 demonstrates the effect of salts on the viscosity-shear rate relationship of sodium hyaluronate. One can see, that 25 mM (0.15%) sodium chloride (about 1/6 of isotonic) completely abolishes the shear rate dependency of the viscosity. Calcium (and presumably other divalent cations) is even more efficient to abolish such dependency: 2 mM (0.022%) CaCl.sub.2 is sufficient.

10 Surprisingly, the addition of isotonic glycerine (2.7%) has little effect on the general shape of the sodium hyaluronate curve with no added salt.

11 The invention illustrated with reference to the following examples, which are of an illustrative nature only, and which are of a non-limitative nature.

12 EXAMPLE 1

13 Isotonic Ophthalmic Solution

14 A solution was prepared containing:

Glycerol		2.75	g
Sodium hyaluronate		0.10	g
Water	up to	100	ml

15 EXAMPLE 2

16 Isotonic Ophthalmic Solution

17 An isotonic solution was prepared containing:

Glycerol		2.75	g
Carbomer 941*		0.03	g
Water	up to	100	ml

*High M.W. Polyacrylate.

18 EXAMPLE 3

19 Isotonic Ophthalmic Solution

20 An isotonic solution was prepared containing:

Glycerol		2.50	g
Carbomer 941*		0.015	g
Sodium hyaluronate		0.015	g
Water	up to	100	ml

*High M.W. Polyacrylate.

21 The viscosity shear rate curves are shown in FIG. 2. It has to be remarked that the exact shape of the curves are very much dependent on the molecular weight of the polymers used and the pH of the solution and may change even from batch to batch.

22 EXAMPLE 4

23 Isotonic Ophthalmic Antiviral Solution:

24 To 100 ml of the solution of Example 1, 2 and 3, there was added:

25 0.1 g Idoxuridine.

26 EXAMPLE 5

27 Isotonic Antiglaucoma Preparation:

28 To 100 ml of the solution of Example 1, 2 and 3, there was added:

29 2 g pilocarpine as polyanion preparation.

30 EXAMPLE 6

31 Isotonic Ophthalmic Antibacterial Preparation:

32 To 100 ml of the solution of Example 1, 2 and 3, there was added:

33 0.5 g Chloramphenicol.

34 EXAMPLE 7

35 Anti-inflammatory Ophthalmin Solution:

36 To 100 ml of the solution of Example 1, 2 and 3, there was added:

37 0.05 g dexamethason sodium phosphate.

38 The addition of drugs decreased the dependency of the viscosity on shear rate, but sufficient dependency remained for comfortable eye drops.

39 In all the examples, the solution was adjusted to about isotonicity and to a pH of slightly above 7.

40 Suitable conventional stabilizers and preservatives can be added and marketed in steril units.

41 A group of 20 patients suffering from dry eye syndrome was treated with the ophthalmic solution of Example 1.

42 With conventional preparations they required more than four applications of eye drops per day.

43 Using the composition of Example 1, the average required decreased to three applications daily.

44 Another average was tested with the Example 3 composition. Only two daily applications were needed.

45 Eye drops containing an anti-inflammatory solution as set out in Example 7 were used for the treatment of inflammations of the eye. The drops were well tolerated and good results were obtained without any irritation of the eye.

46 Relief was very rapid.

47 The combination of a humectant and of a high molecular weight anionic polymer in a suitable aqueous vehicle, which contains only such a quantity of salt as not to interfere with the shear dependence of the eyedrops. Imitates to a large extent the behavior of a tear film.

48 To the best of the knowledge of applicant no such eyedrops are known from the prior art.

CLAIMS:

I claim:

1. An aqueous ophthalmic isotonic moisturizing solution having pronounced non-Newtonian rheological properties;

(i) containing an anionic polymer having molecular weight from about 500,000 to about 4,000,000 at a concentration resulting in a viscosity of not above 150 cp at 1 sec.sup.-1 shear rate,

which decreases to less than 30 cp sec.sup.-1 at 100 sec.sup.-1 shear rate,

(ii) a humectant moisturizing polyol of molecular weight less than about 500, having strong water-holding properties, at essentially isotonic or slightly above or below isotonic concentration,

which solution contains less than 1.5 millimole of monovalent or bivalent salts, not including the salts of the anionic polymer.

2. An ophthalmic solution according to claim 1, where the humectant is glycerol.

3. An ophthalmic solution according to claim 1, where the anionic polymer is a carbomer at a concentration of 0.05% by weight or less.

4. An ophthalmic solution according to claim 1, where the anionic polymer is a polymer having carboxylic groups selected from hyaluronic acid, polyacrylic acids, carbomers and mixtures thereof.

5. An ophthalmic solution according to claim 1, where humectant is 300 to 500 M.W. polyethylene glycol or polypropylene glycol of 300 to 500 M.W.

6. An ophthalmic composition according to claim 3, where the anionic polymer is carbomer 941.

7. An ophthalmic composition according to claim 1, where the anionic polymer is hyaluronic acid, which comprises up to 0.35 by weight of the compositions.

8. An ophthalmic composition according to claim 1, containing in addition an efficient concentration of an antibacterial agent, antiviral agent, antiglaucoma agent or antiinflammatory agent.

9. A method for alleviating the symptoms of dry eye syndrome which comprises applying to the eye an ophthalmic solution as claimed in claim 1.

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L2: Entry 1 of 1 File: USPT May 18, 1993

US-PAT-NO: 5212162
DOCUMENT-IDENTIFIER: US 5212162 A

TITLE: Use of combinations gelling polysaccharides and finely divided drug carrier substrates in topical ophthalmic compositions

DATE-ISSUED: May 18, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 07/ 857673 [PALM]
DATE FILED: March 25, 1992

PARENT-CASE:

This application is a continuation of Application Ser. No. 07/676,146, filed Mar. 27, 1991, now abandoned.

INT-CL: [05] A61K 31/715, A61K 31/70

US-CL-ISSUED: 514/54; 514/57, 514/913, 514/912, 536/1.11, 536/114, 536/123.1, 424/427
US-CL-CURRENT: 514/54; 424/427, 514/57, 514/912, 514/913, 536/1.11, 536/114, 536/123.1

FIELD-OF-SEARCH: 514/54, 514/57, 514/912, 514/913, 536/1.1, 424/427

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4014335	March 1977	Arnold	424/427

☐	4136173	January 1979	Pramoda et al.	424/177
☐	4136177	January 1979	Lin et al.	424/211
☐	4136178	January 1979	Lin et al.	424/211
☐	4505923	March 1985	Hoffman, Jr. et al.	514/912
☐	4861760	August 1989	Mazuel et al.	536/1.1
☐	4911920	March 1990	Jani et al.	514/913
☐	4931279	June 1990	Bawa et al.	424/427
☐	4983585	January 1991	Pennell et al.	514/57

OTHER PUBLICATIONS

Maren et al., Exp. Eye Res., 36: 457-480 (1983).
Maren et al., Exp. Eye Res., 50: 27-36 (1990).
Harris, P. (ed), Food Gels, New York: Elsevier Applied Science, 1990, Ch. 3 (pp. 79-119) and Ch. 6 (pp. 201-232).
McGraw-Hill Dictionary of Scientific and Technical Terms, Third Edition, New York: 1984 p. 1640.

ART-UNIT: 185

PRIMARY-EXAMINER: Wityshyn; Michael G.

ASSISTANT-EXAMINER: Leary; Louise N.

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ABSTRACT:

Ophthalmic compositions comprising combinations of gelling polysaccharides and finely-divided drug carrier substrates which become relatively more viscous on contact with the eye are disclosed. These ophthalmic compositions are both comfortable and long-lasting Ophthalmic compositions further comprising a pharmaceutically active drug are also disclosed, as are methods of use.

27 Claims, 0 Drawing figures
Exemplary Claim Number: 1

BRIEF SUMMARY:

1 BACKGROUND OF THE INVENTION

2 1. Field of the Invention

3 The present invention relates to the use of adjuvants in topical ophthalmic compositions. In particular, this invention relates to the use of a combination of gelling polysaccharides and finely-divided drug carrier substrates in the compositions and a method for the controlled administration of a drug to patients wherein the compositions are administered as liquids which thicken to form gels upon instillation into the eye.

4 2. Description of the Related Art

5 There have been a multiplicity of liquids, ointments, gels and inserts used as vehicles in topical ophthalmic formulations. Liquid compositions for drop-wise instillation to the eye provide for easy formulation, but do not provide an accurate dosage amount, as portions of the liquid are often blinked away during their administration. Ointments and gels, while providing more accurate administration, often interfere with a patient's vision. Ocular inserts, both bioerodible and non-bioerodible, are also available and allow for less frequent administration of drug; however, these inserts require complex and detailed preparation. An additional problem with the non-bioerodible inserts is that they must be removed after use.

6 U.S. Pat. Nos. 4,136,173 (Pramoda, et al.), 4,136,177 (Lin, et al.) and 4,136,178 (Lin, et al.) disclose the use of therapeutic compositions containing xanthan gum and locust bean gum which are delivered in liquid form and which gel upon instillation. In these three patents, the mechanism for transition from liquid to gel is due to a change in pH.

7 U.S. Pat. No. 4,861,760 (Mazuel, et al.) discloses ophthalmological compositions containing gellan gum which are administered as non-gelled liquids and which gel upon instillation due to the change in ionic strength.

8 Commonly assigned U.S. patent application Ser. No. 07/641,214, filed on Jan. 15, 1991, discloses ophthalmic formulations containing carrageenans and furcellarans (hereinafter collectively referred to as "carrageenans") which are administered as partially gelled liquids which gel upon instillation into the eye.

9 SUMMARY OF THE INVENTION

10 The present invention is directed to topical ophthalmic compositions comprising combinations of gelling polysaccharides (defined below) and finely-divided drug carrier substrates (hereinafter "DCS" and defined below) to provide comfort and sustained release of drug to the eye, as well as methods for their use. In addition, the compositions without drug can be administered in order to lubricate the eye or to supplement tears in the treatment of, for example, dry eye. The compositions are administered as liquids or partially gelled liquids (hereinafter collectively referred to as "liquids") which thicken to form gels upon instillation into the eye.

DETAILED DESCRIPTION:

1 DETAILED DESCRIPTION OF THE INVENTION

2 As used herein, the term "gelling polysaccharide" means a polysaccharide capable of a reversible liquid-to-gel transition based on a change in ionic strength or pH. Such factors as a change in temperature, amount and type of DCS, and characteristics and concentrations of drugs or other adjuvants may also affect the ability of the gelling polysaccharides to undergo a liquid-to-gel transition. Suitable gelling polysaccharides include, but are not limited to: xanthan gum, locust bean gum, gellan gum, carrageenans and combinations thereof. These gelling polysaccharides are discussed in detail in U.S. Pat. Nos. 4,136,173, 4,136,177, 4,136,178, 4,861,760, and U.S. patent application Ser. No. 07/641,214, respectively. The contents of these patents and patent applications relating to the gelling polysaccharides cited above are hereby

incorporated by reference herein.

3 The preferred gelling polysaccharides of the present invention are the carrageenans, especially carrageenans with not more than 1.0 sulfate moiety per disaccharide unit such as eucheuma carrageenan and furcellaran. These provide both great contrast in the ratio of gel elastic modulus to viscosity over the temperature ranges of interest, as explained below, as well as limited response to drug counter-ions, especially as to their influence on gellation.

4 The DCS component of the present compositions is added to provide an additional means of controlling release, as well as to prevent the stinging which often occurs with the topical administration of certain drugs, such as betaxolol. As used herein, the term "finely-divided drug carrier substrate" (or "DCS") means finely-divided solids, colloidal particles, or soluble polymers and/or polyelectrolytes which are capable of selective adsorption or binding with drug molecules. Examples of DCS include, but are not limited to: finely divided silica, such as fumed silica, silicates and bentonites; ion exchange resins, which can be anionic, cationic or non-ionic in nature; and soluble polymers, such as, alginic acid, pectin, soluble carrageenans, carbopol, and polystyrene sulfonic acid. Preferred DCS are the ion exchange resins. Some resins which are used in chromatography make ideal DCS for binding drugs in the compositions of the present invention.

5 Ion exchange resins are typically in the form of beads which may be either porous or non-porous. Porous beads can be advantageous because they provide more surface area for the placement of functional groups, which lead to increased drug binding and improved sustained release.

6 Functional groups which may be added to the resin beads or polymers include acids, bases or neutral hydrophobic or hydrophilic groups to influence the binding of the drug. Specific functional groups may include, but are not limited to: sulfonic acid, carboxylic acid, phosphoric acid, aromatic groups such as phenyl or pyridinium, alkyl carbon chains, polyethylene oxide, polypropylene oxide, polypropylene oxide, carboxymethyl, sulfopropyl, polyglycol and combinations thereof. The choice of functional group will depend on the drugs to be delivered, especially their charge at the pH of the composition. For example, drugs with a positive charge at the desired composition pH will typically be formulated with resins having cationic functional groups at the composition pH.

7 Cationic exchange resins are characterized as either strongly acidic, such as those having sulfonic acid functionality, or weakly acidic, such as those having carboxylic acid functionality. Anionic exchange resins are characterized as either strongly basic, containing, for example, quaternary ammonium functionalities, or weakly basic, containing, for example, amines. Non-ionic resins may have any of a variety of functionalities whose charges offset each other (i.e., zwitterions), resulting in a neutral resin, or they may be comprised of non-ionic polymers having any of a variety of hydrophilic functional groups.

8 The choice of resin functional group density (hereinafter "charge density") will also depend on the nature of the drug to be delivered. For example, drugs having multiple sites capable of binding or adhering to a resin (multiple resin binding sites) such as tobramycin, are strongly attracted to resins having relatively high charge densities, such as Amberlite. Such combinations would not necessarily be desirable, since the resin-drug affinity would be so great that little or no drug would be available to the eye in a reasonable

time period. Therefore, drugs having multiple resin binding sites are preferably combined with resins having relatively low charge densities, such as carboxymethyl Sephadex. This will provide for a composition wherein the drug is available to the eye, but over a period of time. On the other hand, other drugs which do not have multiple resin binding sites are preferably combined with resins having a relatively high charge density in order to achieve a sustained release.

9 The size of the DCS can be important, both with respect to mode of action and comfort. The average particle size of the typical commercially available form of the DCS material of choice, an ion exchange resin, is about 40 to about 150 microns. Such particles are most conveniently reduced to a particle size range of about 1.0 to about 25.0 microns, preferably between about 1.0 and 10.0 microns, by ball milling, according to known techniques. In the alternative, small particles may be synthesized in the optimal size range of 3-7 microns. Although this procedure can be more expensive, it is superior in providing a more uniform and narrow distribution of sizes in the preferred range.

10 The DCS component is present in the compositions of the present invention at a level in the range of about 0.05 to about 10.0% by weight. For particulate DCS, the average particle size diameter ranges from 1 to 20 microns. The amount of DCS and its characteristics (e.g., amount of cross-linking, particle size) may be varied in order to produce the desired time-release profile for the chosen drug. A long time-release profile, desirable for a drug having a short biological half-life, such as apraclonidine, may be achieved by using a large excess of DCS (i.e., the number of DCS binding/exchange sites is several times that of the drug(s) being delivered). An intermediate release profile, suggested for a drug such as pilocarpine, with a reasonably good half-life (4 hours), may be obtained by using a small excess of DCS or no excess DCS (i.e., the number of DCS binding sites is equivalent to that of the drug(s) being delivered). For drugs which have serious side effects, such as betaxolol, a preferred release profile is usually a rapid initial release spike, to release an amount of drug effective to cross the therapeutic threshold, followed by a sustained release tail, to maintain the therapeutic effect but to reduce or eliminate side effects. This may be achieved by using an excess of drug (as compared to the number of DCS binding sites).

11 DCS materials which can be used on the composition of the present invention may include, but are not limited to: fumed silica, e.g., Cab-O-Sil (Cabot Corporation, Boyertown, Penna.); silicates, e.g., Veegums (R. T. Vanderbilt, Norwalk, Conn.), Gelwhite (ECC American, Inc., Dover, Ohio); bentonites, e.g., bentonite (native hydrated colloidal aluminum silicate clay), Claytone (ECC American, Inc., Dover, Ohio), Macaloid (NL Chemicals, Hightstown, N.J.), Bentone EW (NL chemical, Hightstown, N.J.); polystyrene/ divinylbenzene, e.g. Amberlite IRP-69 (Rohm & Haas, Philadelphia, Penna.) and RCX-20 (Hamilton, Reno, Nev.); polymethacrylic acid, e.g. Amberlite IRP-64 (Rohm & Haas); hydroxymethylmethacrylate (HEMA), e.g. HEMA-IEC BIO 1000 SB (Alltech Associates, Deerfield, Ill.); cross-linked dextran, e.g. Sephadex (Dow Chemicals, Midland, Mich.); and alginic acid.

12 The compositions of the present invention may be formulated in many ways, for example 1) a liquid formulation, wherein the composition is a low viscosity liquid which becomes a high viscosity liquid or a gel upon instillation in the eye; 2) a stiff gel formulation, wherein the composition is a weak gel which becomes a stiffer gel in the eye; and 3) a thixotropic formulation, wherein the composition is a viscous liquid when shaken and a gel when left standing for a period of time.

13 The different types of formulations discussed above exhibit different physical

characteristics. For the sake of clarity and for ease of a reference in the discussion below, "pre-dosed" refers to a formulation's characteristics before topical administration to the eye and "post-dosed" refers to a formulation's characteristics after administration into the eye.

14 The liquid formulations have a pre-dosed viscosity in the range of about 1 to about 500 centipoise (cps), with about 1 to about 200 cps preferred, and about 1 to about 100 cps most preferred. If the liquid formulations do not form a gel in the eye, but simply become more viscous, the post-dosed viscosity will be greater than about 50 cps, preferably greater than about 150 cps, and most preferably greater than about 300 cps. If the liquid formulations do form a gel in the eye, the gel will have a modulus of elasticity (Young's modulus) in the range of about 1.times.10.sup.4 to about 5.times.10.sup.5 dynes/cm.sup.2, with about 2.times.10.sup.4 to about 5.times.10.sup.5 dynes/cm.sup.2 preferred and about 5.times.10.sup.4 to about 5.times.10.sup.5 dynes/cm.sup.2 most preferred.

15 The stiff gel formulations have a pre-dosed modulus of elasticity in the range of about 1.times.10.sup.4 to about 3.times.10.sup.5 dynes/cm.sup.2, with about 2.times.10.sup.4 to about 2.times.10.sup.5 dynes/cm.sup.2 preferred and about 5.times.10.sup.4 to about 1.times.10.sup.5 dynes/cm.sup.2 most preferred. The post-dosed stiff formulations are gels and will have a modulus of elasticity in the range of about 1.times.10.sup.4 to about 2 .times.10.sup.6 dynes/cm.sup.2, with 1.times.10.sup.5 to about 7.times.10.sup.5 dynes/cm.sup.2 preferred and about 2.times.10.sup.5 to about 5.times.10.sup.5 dynes/cm.sup.2 most preferred.

16 The thixotropic formulations, when shaken, have a pre-dosed viscosity in the range of about 1 to about 5000 cps, with about 50 to about 1000 cps preferred and about 200 to about 500 cps most preferred. The pre-dosed gel forms of the thixotropic formulations have a modulus of elasticity in the range of about 1.times.10.sup.4 to about 2.times.10.sup.5 dynes/cm.sup.2 , with about 2.times.10.sup.4 to about 1.times.10.sup.5 dynes/cm.sup.2 preferred and about 3.times.10.sup.4 to about 7.times.10.sup.4 dynes/cm.sup.2 most preferred. The post-dosed gels will have a modulus of elasticity in the range of about 1.times.10.sup.4 to about 2.times.10.sup.6 dynes/cm.sup.2 , with about 2.times.10.sup.4 to about 1.times.10.sup.5 dynes/cm.sup.2 preferred and about 3.times.10.sup.4 to about 7.times.10.sup.4 dynes/cm.sup.2 most preferred.

17 Suitable ophthalmic agents ("drugs") which can be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to: glaucoma agents, such as betaxolol, pilocarpine and carbonic anhydrase inhibitors; dopaminergic antagonists; post-surgical antihypertensive agents, such as a para-amino clonidine (apraclonidine); anti-infectives, such as ciprofloxacin; non-steroidal and steroidal anti-inflammatories, such as suprofen, ketorolac and tetrahydrocortisol; prostaglandins; proteins; growth factors, such as EGF; and anti-allergics. Compositions of the present invention may also include combinations of ophthalmic agents. In a formulation without the use of ophthalmic agents, the present invention may also serve to supplement tears in the prevention or treatment of dry eye.

18 The compositions of the present invention can include other components, for example, ophthalmically acceptable buffers, preservatives, and tonicity agents.

19 In general, for water-soluble drugs, the compositions of the present invention are formulated such that the DCS is added to the solution prior to the

addition of drug (if any) and the gelling polysaccharide is added last, after all the other ingredients have been mixed. Where the drug to be included in the compositions of the present invention has a low solubility, it is preferred that the drug be added last, that is, after the addition of the gelling polysaccharide. In certain cases, it may also be preferred that the drug be separately sterilized (e.g., with radiation) and aseptically added to the other ingredients, which have been autoclaved according to the sterilization procedure described below.

20 Sterilization of the compositions can be accomplished by autoclaving. It is well known that an order of magnitude reduction in sterilization time is achieved for every 10.degree. C. rise in sterilization temperature. As the gelling polysaccharides tend to decompose and caramelize when heated, sterilization at higher temperatures with lower sterilization time is generally preferred. The preferred temperature range is greater than about 130.degree. C., with a sterilization time of less than about 3 minutes when the pH of the composition is more than about 6. In the alternative, aseptic combinations of drug and gelling polysaccharide can be utilized when the hydration of resin results in chemical instability of drug or of the drug/DCS complex. In those instances where the final pH of the composition is less than 6, it is preferred that sterilization take place at pH close to 7.4, then to adjust the pH by aseptic means to its final value.

21 The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

22 EXAMPLE 1

23 The following are examples of stiff gel formulations:

Ingredients	Percent by weight/volume										
	A	B	C	D	E	F	G	H	I	J	K
Eucheuma	--	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	--
Carrageenan.sup.1											
Furcellaran.sup.2	0.6	--	--	--	--	--	--	--	--	--	0.6
Na.sub.2 HPO.sub.4	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	--	--
Mannitol	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Acid Amberlite	5.0	5.0	3.0	--	--	--	--	--	5.0	--	--
RCX-20	--	--	--	5.0	--	--	--	--	--	--	--
Cellulose Phosphate	--	--	--	--	5.0	--	--	--	--	--	--
Carboxymethyl Sephadex	--	--	--	--	--	4.0	--	--	--	--	--
Sulfopropyl Sephadex	--	--	--	--	--	--	7.2	--	--	--	--
Amberlite CG400	--	--	--	--	--	--	--	5.0	--	--	--
Bentonite	--	--	--	--	--	--	--	--	--	2.0	--

Cab-O-Sil	--	--	--	--	--	--	--	--	--	--	1.0
S-Betaxolol (free base)	--	0.5	--	--	--	--	--	--	--	--	--
Apraclondine	--	--	1.0	--	--	--	--	--	--	1.0	--
Pilocarpine	--	--	--	1.0	--	--	--	--	--	--	--
Tobramycin	--	--	--	--	2.0	2.0	2.0	2.0	--	--	--
Suprofen	--	--	--	--	--	--	--	--	1.0	--	--
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS

.sup.1 Extracted from Eucheuma gelatinae.
.sup.2 Extracted from Furcellaria fastigata.

24 Preparation of Formulation B

25 The following procedure was utilized to prepare a 50 milliliter (ml) batch of Formulation B.

26 Approximately 30 ml of water (about 2/3 of the final volume), 0.051 grams (g) of Na.sub.2 HPO.sub.4 (0.1% w/v) and 1.750 g of mannitol (3/5% w/v) were added to a beaker equipped with a magnetic stir bar. The mixture was stirred until the ingredients were dissolved, then 8.357 g of rinsed Acid Amberlite (corresponding to 2.5 g dry weight) was added and the mixture stirred for another 15 minutes (min), until the Amberlite was uniformly mixed; that is, until there were no lumps. The pH of the mixture was raised from 1.96 to 2.51 by the addition of 10N NaOH. After the pH adjustment, 0.24 g of S-betaxolol (free base) was added and mixture stirred approximately 1/2 hour without adjusting pH. The pH of the mixture was then adjusted to 3.34 by addition of 1N NaOH. The mixture was stirred overnight (at least 12 hours) to ensure that the S-betaxolol was adequately bound to the Acid Amberlite. The pH of the mixture was then raised to 7.40 with 10N NaOH and water added to bring the final volume to 50 ml. The mixture was then heated to 75.degree. C. and 1.000 g of eucheuma carrageenan (2%) added. The mixture was then stirred, heated, and maintained at 90.degree. C. for a half hour. When the mixture was removed from the heat, the osmolality was checked. The final osmolality was 308 milliOsmolal (mOsm).

27 The mixture was sterilized in an autoclave at 130.degree. C. for 3 minutes in containers having radii no greater than 1 centimeter (cm). After sterilization, the containers were removed and allowed to air cool to room temperature.

28 EXAMPLE 2

29 The following are examples of thixotripic gel formulations:

Ingredients	Percent by weight/volume									
	A	B	C	D	E	F	G	H	I	J
Eucheuma	--	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

Carrageenan										
Gellan Gum	0.6	--	--	--	--	--	--	--	--	--
Na.sub.2 HPO.sub.4	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mannitol	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Acid Amberlite	5.0	5.0	3.0	--	--	--	--	--	5.0	5.0
RCX-20	--	--	--	5.0	--	--	--	--	--	--
Cellulose Phosphate	--	--	--	--	5.0	--	--	--	--	--
Carboxymethyl Sephadex	--	--	--	--	--	4.0	--	--	--	--
Sulfopropyl Sephadex	--	--	--	--	--	--	7.2	--	--	--
Amberlite CG400	--	--	--	--	--	--	--	5.0	--	--
S-Betaxolol (free base)	--	0.5	--	--	--	--	--	--	--	--
Apraclonidine	--	--	1.0	--	--	--	--	--	--	--
Pilocarpine	--	--	--	1.0	--	--	--	--	--	--
Tobramycin	--	--	--	--	2.0	2.0	2.0	2.0	--	--
Suprofen	--	--	--	--	--	--	--	--	1.0	--
ALO4414A.sup.1	--	--	--	--	--	--	--	--	--	2.0
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS

.sup.1
(+)-4-Ethylamino-2,3-dihydro-4H-2-methylthieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide HCl.

30 The compounding procedure for these formulations are similar to the procedure detailed in Example 1, above.

31 EXAMPLE 3

32 The following are examples of liquid formulations:

	Percent by weight/volume							
Ingredients	A	B	C	D	E	F	G	H
Eucheuma Carrageenan	0.3	--	0.3	--	0.3	0.3	--	--
Kappa Carrageenan.sup.1	--	0.5	--	--	--	--	0.5	--
Furcellaran	--	--	--	0.3	--	--	--	0.3
Na.sub.2 HPO.sub.4	0.1	0.1	0.1	0.1	0.1	--	0.1	--
Mannitol	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

Acid Amberlite	5.0	5.0	5.0	5.0	5.0	--	--	--
Claytone	--	--	--	--	--	2.0	--	--
Gelwhite	--	--	--	--	--	--	2.0	--
Bentonite	--	--	--	--	--	--	--	2.0
S-Betexolol (free-base)	0.5	--	--	--	--	--	0.5	--
Pilocarpine	--	--	--	--	1.0	1.0	--	--
ALO4414A	--	--	2.0	--	--	--	--	--
Water	QS	QS	QS	QS	QS	QS	QS	QS

.sup.1 Extracted from Eucheuma cottonii.

33 Compounding procedures are similar to the procedure detailed in Example 1, above.

CLAIMS:

What is claimed is:

1. A topical ophthalmic composition comprising a gelling polysaccharide and a finely-divided drug carrier substrate, wherein the concentration of said gelling polysaccharide allows the composition to be administrable as a drop which gels upon instillation to the eye.

2. The composition of claim 1 wherein the finely-divided drug carrier substrate is an ion exchange resin.

3. The composition of claim 1 wherein the gelling polysaccharide concentration is between 0.1% and 3.0% by weight/volume and the concentration of the finely-divided drug carrier substrate is between 0.05% and 10.0% by weight/volume.

4. The composition of claim 1 wherein the gelling polysaccharide is selected from the group consisting of xanthan gum, locust beam gum, gellan gum, and carrageenan.

5. The composition of claim 4 wherein the gelling polysaccharide is gellan gum.

6. The composition of claim 4 wherein the gelling polysaccharide is a carrageenan having not more than 1.0 sulfate moiety per disaccharide repeating unit.

7. The composition of claim 6 wherein said carrageenan is eucheuma carrageenan.

8. The composition of claim 6 wherein said carrageenan is furcellaran.

9. The composition of claim 1 wherein the pre-dosed viscosity thereof is between 1 and 500 cps and the post-dosed viscosity is greater than 50 cps.

10. The composition of claim 1 wherein the pre-dosed viscosity thereof is between 1 and 500 cps and the post-dosed gel has a modulus of elasticity between 1.times.10.sup.4 and 5.times.10.sup.5 dynes/cm.sup.2.

11. The composition of claim 1 wherein the pre-dosed modulus of elasticity

thereof is between 1.times.10.sup.4 and 3.times.10.sup.5 dynes/cm.sup.2 and the post-dosed modulus of elasticity thereof is between 1.times.10.sup.4 and 2.times.10.sup.6 dynes/cm.sup.2.

12. The composition of claim 1 wherein the composition is thixotropic, having a pre-dosed modulus of elasticity between 1.times.10.sup.4 and 2.times.10.sup.5 dynes/cm.sup.2 and, after shaking, a pre-dosed viscosity between 1 and 5000 cps and having a post-dosed modulus of elasticity between 1.times.10.sup.4 and 2.times.10.sup.6 dynes/cm.sup.2.

13. The composition of claim 1 further comprising an ophthalmic agent.

14. The composition of claim 13 wherein the ophthalmic agent is para-amino clonidine.

15. The composition of claim 13 wherein the ophthalmic agent is a carbonic anhydrase inhibitor.

16. The composition of claim 15 wherein the carbonic anhydrase inhibitor is (+)-4-ethylamino-2,3-dihydro-4H-2-methylthieno-[3,2-e]1,2-thiazine-6-sulfo namide-1,1-dioxide or a pharmaceutically acceptable salt thereof.

17. A method of delivering an ophthalmic agent to the eye which comprises topically administering a composition comprising: an ophthalmic agent, a gelling polysaccharide, and a finely-divided drug carrier substrate, wherein the concentration of said gelling polysaccharide allows the composition to be administrable as a drop which gels upon instillation to the eye.

18. The method of claim 17 wherein the finely-divided drug carrier substrate is an ion exchange resin.

19. The method of claim 17 wherein the gelling polysaccharide concentration is between 0.1% and 3.0% by weight/volume and the finely-divided drug carrier substrate concentration is between 0.05% and 10.0% by weight/volume.

20. The method of claim 17 wherein the gelling polysaccharide is selected from the group consisting of xanthan gum, locust bean gum, gellan gum, and carrageenan.

21. The method of claim 20 wherein the gelling polysaccharide is gellan gum.

22. The method of claim 20 wherein the gelling polysaccharide is a carrageenan having not more than 1.0 sulfate moiety per disaccharide repeating unit.

23. The method of claim 22 wherein said carrageenan is eucheuma carrageenan.

24. The method of claim 22 wherein said carrageenan is furcellaran.

25. The method of claim 17 wherein the ophthalmic agent is para-amino clonidine.

26. The method of claim 17 wherein the ophthalmic agent is a carbonic anhydrase inhibitor.

27. The method of claim 26 wherein the carbonic anhydrase inhibitor is (+)-4-ethylamino-2,3-dihydro-4H-2-methylthieno-[3,2-e]1,2-thiazine-6-sulfo namide-

1,1-dioxide or a pharmaceutically acceptable salt thereof.